



Title	Impact of body mass index on mortality in heart failure patients(本文)
Author(s)	滝口, 舞
Citation	
Issue Date	2017-03-24
URL	http://ir.fmu.ac.jp/dspace/handle/123456789/955
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DOI	
Text Version	ETD

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Impact of body mass index on mortality in heart failure patients

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A short title: BMI predicts adverse prognosis of HF

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Total word count of manuscript: 2536 words

Total number of tables and figures: 4 tables and 1 figure

Abstract

Background Higher body mass index (BMI) is associated with incident heart failure (HF), but paradoxically associated with better prognosis, recognized as the obesity paradox in HF. However, the impact of BMI on detailed prognosis on HF and the mechanism of obesity paradox remain still unclear.

Methods We researched consecutive 648 patients admitted for HF: Underweight (BMI < 18.5 kg/m², n=86), Normal ($18.5 \leq \text{BMI} < 25$, n=380), Overweight ($25 \leq \text{BMI} < 30$, n=147), and Obese ($30 \leq \text{BMI}$, n=35), and compared the results from their laboratory tests and echocardiography. We also followed cardiac and all-cause mortality.

Results Obese group had a higher prevalence of obesity-related co-morbidity (hypertension, diabetes, dyslipidemia), however, tumor necrosis factor- α , adiponectin, troponin T, and systolic pulmonary arterial pressure were higher in the Underweight group than in the other groups ($P < 0.05$, respectively). Left and right ventricular systolic function did not differ among the groups. In the Kaplan-Meier analysis, cardiac and all-cause mortality were significantly higher in the Underweight group than in the other groups. Importantly, in the Cox proportional hazard analyses after adjusting for known risk factors, BMI was an independent predictor of cardiac and all-cause mortality ($P < 0.01$, respectively) in HF patients.

Conclusions BMI was an independent predictor of cardiac death and all-cause mortality in HF patients. Furthermore, lower BMI was associated with higher circulating levels of tumor necrosis factor- α , adiponectin and troponin T, and higher systolic pulmonary arterial pressure.

Keywords heart failure, body mass index, tumor necrosis factor- α , adiponectin, troponin T, right heart function, prognosis

Introduction

Body mass index (BMI) is a surrogate measure of body fat and may also reflect lean body mass and the validity of obesity and cachexia, and is associated with the prognosis of heart failure (HF).[1-3] Although obesity is associated with the onset of cardiovascular disease including HF, [4, 5] it is paradoxically associated with better prognosis, recognized as “obesity paradox” in HF.[1, 3, 6, 7] Clark et al. presented that higher BMI was associated with better prognosis in both male and female HF patients, although fat distribution varies by gender.[7] Both higher BMI and circumference were associated with better prognosis in HF.[7] In a meta-analysis, Oreopoulous et al. reported that overweight and obese HF patients had a reduction in all-cause mortality (-16% and -33%, respectively) compared with HF patients with normal BMI.[8] However, the mechanism of the obesity paradox remains still unclear.[6] On the other hand, malnutrition,[9] wasting,[10] weight loss[11] and cachexia[12] are associated with poor prognosis in HF patients. Malnutrition is common in patients with HF and is associated with increased right atrial pressure and tricuspid regurgitation.[9] HF patients with right ventricular (RV) dysfunction had lower fat mass and body weight loss.[12] On another note, several factors such as RV systolic function,[13] pulmonary arterial pressure,[13] renin-angiotensin-aldosterone system (RAS), sympathetic nervous system,

cytokines ((tumor necrosis-factor) $\text{TNF-}\alpha$, [14] adiponectin [15-17]), and cardiac troponin T [18] are the reported predictors of HF patients, and are considered to be related with body composition (obesity and cachexia).

The features of HF related with BMI from the viewpoint of comprehensive status and the impact of BMI on detailed all-cause mortality in HF remain unclear. Therefore, the aim of the present study was to investigate the association of body mass index with 1) cardiac function (especially right heart function), 2) neurohumoral factors ($\text{TNF-}\alpha$, adiponectin, noradrenalin, plasma renin activity, renin concentration, and aldosterone), 3) the presence of co-morbidities (hypertension, diabetes, dyslipidemia, chronic kidney disease, atrial fibrillation, and anemia), and 4) the prognosis (cardiac, non-cardiac, and all-cause mortality).

Methods

Subjects and study protocol

This was a prospective observational study which enrolled consecutive symptomatic HF patients who were hospitalized because of decompensated HF, and discharged from Fukushima Medical University between 2009 and 2012. The diagnosis of decompensated HF was defined based on the Framingham criteria.[19] Patients with acute coronary syndrome, pulmonary thromboembolism, primary pulmonary hypertension, dialysis, and documented cancer were excluded. Finally, we analyzed 648 patients. These patients were divided into four groups based on BMI stratified by World Health Organization criteria for obesity (Underweight $< 18.5 \text{ kg/m}^2$, Normal 18.5 to 25 kg/m^2 , Overweight 25 to 30 kg/m^2 , and Obese $\geq 30 \text{ kg/m}^2$).[8] We compared the clinical features and results from several examinations of each group, such as laboratory tests and echocardiography, performed before discharge. Length of HF was defined as of time from first diagnosis of HF to present hospital admission. Hypertension was defined as the recent use of antihypertensive drugs, a systolic blood pressure $\geq 140 \text{ mmHg}$, and/or a diastolic pressure $\geq 90 \text{ mmHg}$. Diabetes was defined as the recent use of insulin or antidiabetic drugs, a fasting blood glucose value of $\geq 126 \text{ mg/dL}$, and/or a hemoglobin A_{1c} value of $\geq 6.5\%$. Dyslipidemia was defined as the recent use of

cholesterol-lowering drugs, a triglyceride value of ≥ 150 mg/dL, a low-density lipoprotein cholesterol value of ≥ 140 mg/dL, and/or a high-density lipoprotein cholesterol value of <40 mg/dL. Estimated glomerular filtration rate (eGFR) was measured by the Modification of Diet in Renal Disease formula.[20] Anemia was defined as hemoglobin of <12.0 g/dl in females and <13.0 g/dl in males.[21] Reduced left ventricular ejection fraction (LVEF) was defined as less than 50%. Smoker was defined as past or current smoker. The primary outcome of our study was all-cause mortality. Patients were followed up for cardiac death, non-cardiac death, and all-cause mortality. Non-cardiac death included death due to stroke, respiratory failure, infection, sepsis, cancer, digestive haemorrhage, and etc. Survival time was calculated from the date of discharge until the date of death or last follow-up. Status and dates of deaths were obtained from the patients' medical records. If these data were unavailable, status was ascertained by a telephone call to the patient's referring hospital physician. Written informed consent was obtained from all study subjects. The study protocol was approved by the ethical committee of Fukushima Medical University. The investigation conforms with the principles outlined in the Declaration of Helsinki. Reporting of the study conforms to STROBE along with references to STROBE and the broader EQUATOR guidelines.[22]

Echocardiography

Echocardiography was performed blindly by an experienced echocardiographer using the standard techniques. Echocardiographic parameters investigated included left ventricular (LV) volume, LVEF, left atrial volume, the ratio of early transmitral flow velocity to mitral annular velocity (mitral valve E/e'), inferior vena cava diameter, systolic pulmonary artery pressure (SPAP), [23] right atrial end systolic area, right ventricular (RV) area, right ventricular fractional area change (RV-FAC), tissue Doppler-derived tricuspid lateral annular systolic velocity (tricuspid valve S'), and the ratio of the peak transtricuspid velocity during early diastole to the peak tricuspid valve annular velocity during early diastole (tricuspid valve E/e'). [23] LVEF was calculated using a modification of Simpson's method. Mitral valve E/e' was calculated by transmitral Doppler flow and tissue Doppler imaging. SPAP was calculated by adding the right atrial pressure (estimated by the diameter and collapsibility of the inferior vena cava) to the systolic trans tricuspid pressure gradient. [13, 23] The RV-FAC, defined as $(\text{end diastolic area} - \text{end systolic area}) / \text{end diastolic area} \times 100$, is a measure of right ventricular systolic function. [23] Tricuspid valve E/e' was calculated by transtricuspid Doppler flow and tissue Doppler imaging. All recordings were performed on ultrasound

systems (ACUSON Sequoia, Siemens Medical Solutions USA, Inc., Mountain View, CA, USA).

Measurement of levels of TNF- α , adiponectin, and troponin T

A blood sample was obtained from each patient at Fukushima Medical University before discharge under fasting state. The high-sensitive troponin T level was measured using electrochemiluminescence immunoassay (Elecsys Troponin T hs, Roche Diagnostics Ltd., Rotkreuz, Switzerland).[18] TNF- α was measured, based on the method of solid phase chemiluminescent ELISA using immuno assay kit (Quanti Glo ELISA Human TNF- α Immunoassay, R&D Systems, Minneapolis, USA). Total serum adiponectin was based on the method of latex agglutination turbidimetric immunoassay, using immuno assay kit (Human Adiponectin Latex Immunoassay, LSI Medience, Tokyo, Japan).

Statistical analysis

Normally distributed data are presented as mean \pm SD, and non-normally distributed data are presented as median (inter-quartile range). Categorical variables are expressed as numbers and percentages. Univariate comparisons among groups were performed

using chi-square analysis, analysis of variance, and the Kruskal-Wallis test, as appropriate. Kaplan-Meier method was used for presenting the event-free rate and the log-rank test was used for initial comparisons. Univariable and multivariable Cox proportional hazard analyses were used to analyze predictors of events and to adjust for confounding factors. To prepare for potential confounding, we introduced the following factors, known to affect the risk of cardiac or all-cause mortality in HF patients: age, gender, over two past hospitalizations, length of HF over two years, systolic blood pressure, New York Heart Association (NYHA) functional class III or IV, presence of ischemic etiology, smoking, hypertension, diabetes, dyslipidemia, atrial fibrillation, chronic kidney disease, anemia, hyposodium (<135 mEq/l), reduced LVEF ($<50\%$), and use of RAS inhibitor, β -blocker, statin, anti-diabetic drug, or inotropics. A value of $P < 0.05$ was considered significant for all comparisons. These analyses were performed using a statistical software package (SPSS ver. 21.0, IBM, Armonk, NY).

Results

Clinical features are compared among 4 groups (**Table 1**). As expected, the Obese group had a higher prevalence of obesity-related co-morbidity (hypertension, diabetes, dyslipidemia), smokers and ischemic etiology, higher levels of blood pressure. On the other hand, the Underweight group had higher age, a greater likelihood of having a history of over two past hospitalizations, higher presence of NYHA class III or IV, less use of RAS inhibitor, statin, or antidiabetic drugs, higher presence of anemia and inotropic use. **Table 2** shows comparisons of laboratory data among 4 groups. Levels of hemoglobin, sodium, glucose, insulin, hemoglobin A1c, and triglycerides in Obese group were higher than Underweight group. On the other hand, levels of B-type natriuretic peptide, high density lipoprotein, troponin T, TNF- α , and adiponectin in Underweight group were higher than Obese group. In contrast, plasma noradrenalin, plasma renin activity, rennin concentration and aldosterone did not differ among the four groups. Echocardiographic parameters are summarized in **Table 3**. Left ventricular wall thickness and right atrial and ventricular diameter in Obese group were higher than Underweight group. On the other hand, SPAP was higher in Underweight group than Obese group. In contrast, LVEF and RV-FAC did not differ among the four groups.

During the follow-up period (mean 737 days), there were 68 cardiac deaths and 68 non-cardiac deaths. Details of cardiac and non-cardiac deaths were as follows: heart failure deaths (n=49), ventricular fibrillation (n=19), cancer (n=21), respiratory failure and/or pneumonia (n=16), infection/sepsis (n=10), stroke (n=7), digestive hemorrhage (n=4), aneurysm (n=4), renal failure (n=3), and others (n=3). As shown in Figure 1, the event free rates from cardiac death and all-cause mortality were significantly lower in the Underweight group than in the other groups. Furthermore, non-cardiac death tended to be higher in the Underweight group than in the Obese group.

The Cox proportional hazard model was used to examine prognostic value of BMI in HF patients (**Table 4**). In the multivariable analysis, BMI was an independent predictor of cardiac and all-cause mortality ($P<0.01$, respectively) after adjusting for potential confounding factors (models 1-4) including age, gender, history of over two past hospitalizations, length of HF over two years, systolic blood pressure, NYHA class III or IV, presence of ischemic etiology, smoking, hypertension, diabetes, dyslipidemia, atrial fibrillation, chronic kidney disease, anemia, hyposodium, reduced LVEF, use of RAS inhibitor, β -blocker, statin, anti-diabetes drug, or inotropic.

In addition, BMI was an independent predictor of all-cause mortality when we excluded the Underweight group (hazard ratio 0.937, 95% CI 0.881-0.995). We

analyzed separately HF patients with coronary artery disease (CAD; n=158) and non-CAD (n=490). The rates of all-cause mortality were significantly higher in the Underweight group than in the other groups in both CAD and non-CAD group (P<0.001 and P=0.008, respectively).

Discussion

To the best of our knowledge, the present study is the first to show the impact BMI has, not only for predicting cardiac mortality, but also for predicting all-cause mortality in hospitalized HF patients with regard to comprehensive status, including co-morbidity, cardiac function, RAS, sympathetic nervous system, TNF- α , adiponectin, and troponin T. It was found that BMI was an independent predictor of cardiac and all-cause mortality in HF patients. Underweight patients' conditions were associated with higher TNF- α , adiponectin, troponin T, and pulmonary arterial systolic pressure. These data suggest the mechanism by which BMI impacts the mortality of HF patients.

Obesity (higher BMI) is a global epidemic strongly associated with the development of a broad array of cardiovascular diseases. Obesity has several adverse effects on 1) hemodynamics (increased arterial pressure, LV wall stress, and pulmonary hypertension), 2) cardiac structure (LV hypertrophy, left atrial enlargement, and RV hypertrophy), 3) inflammation (increased C-reactive protein and TNF- α), 4) neurohumoral abnormalities (insulin resistance and hyperinsulinemia, leptin insensitivity, reduced adiponectin, activation of RAS and sympathetic nervous system), and 5) cellular disintegrity (hypertrophy, apoptosis, and fibrosis).[6] Concordant with these mechanisms as expected, our obese group had: 1) higher prevalence of

obesity-related illness (hypertension, diabetes, dyslipidemia), insulin resistance, and ischemic etiology, and 2) higher left ventricular wall thickness and right atrial and ventricular diameters. However, a higher BMI has been reported as “protective” against cardiovascular events. The “obesity paradox” is recognized in HF.[1] Excess adiposity may reflect a metabolic sink capable of resisting catabolic demands in HF.[24-26] On the other hand, cardiac cachexia (lower BMI) is related to hemodynamic alterations of HF,[9, 27] and the following neurohumoral and cytokine responses,[28] have in turn been implicated in gastrointestinal function,[29] liver function,[30] anorexia,[27] hypermetabolism, and changed substrate utilization in tissues.[31] Lower BMI is associated with negative energy balance, systemic inflammation/catabolism (e.g., TNF- α and catecholamine), decreased lean and fat mass, and poorer prognosis in HF.[32] Body weight loss in patients with advanced HF is associated with an increased risk of death.[14] HF-related cachexia is related to RV impairment[9, 33] rather than LV impairment.[34, 35] Increased right heart filling pressure has been linked to body fat depletion[9] and low BMI.[33] However, the mechanisms of the “obesity paradox” in HF remain still unclear and are somewhat difficult to understand. Several potential mechanisms are as follows: 1) nonpurposeful weight loss, greater metabolic reserves, less cachexia, protective cytokines, earlier symptom presentation, attenuated response to

RAS, high blood pressure leading to more HF medications, different etiology of HF, increased muscle mass and muscular strength, and implications related to cardiac rehabilitation.[6]

Higher TNF- α and excess catecholamine are linked to cachexia in HF with reduced LV function.[14, 28] Moreover, increased adiposity may protect mitochondrial function during pressure overload HF, suggesting that BMI not only reflects cachexia and inflammation, but also may be a marker of improved mitochondrial function in HF. Adiponectin is an abundant protein that is secreted primarily from adipose tissue, with concentrations that are inversely associated with obesity.[36] Although adiponectin is considered to be protective against cardiovascular disease,[37-39] its higher levels have paradoxically been associated with worse outcomes among patients with acute coronary syndrome[40] and HF.[15, 16] Higher adiponectin was also reportedly associated with severity of HF,[16, 17] RV dysfunction, and cachexia in HF patients.[12] It has been reported that SPAP is an independent predictor of adverse prognosis in HF patients.[13, 41] Elevated circulating levels of troponins are associated with inflammation[42], presence of non-cardiac co-morbidities,[43] and adverse all-cause mortality.[18] Our present data that the Underweight group had poorer prognoses accompanied by higher

levels of troponin T, TNF- α , adiponectin and SPAP were concordant with previous studies.[12, 13, 15, 18, 28]

Study strengths and limitations

Our study differs from previous studies[1-3] in many ways. For instance, we presented detailed all-cause mortality in HF patients. Importantly, we also showed the association of underweight HF with TNF- α , adiponectin, troponin T, and heart function. Several limitations remain in the present study. First, it was a prospective analysis of a single institution. The number of subjects was relatively small. Hence, prospective studies with a larger population are needed. However, diagnosis of HF was accurately made by our experienced cardiologists using the Framingham criteria. Second, we evaluated RV function and SPAP using echocardiography unless we used right heart catheterization. However, this procedure is not routinely performed. Third, levels of plasma renin activity, concentrations of renin and aldosterone might be affected by taking RAS inhibitors.

Conclusions

BMI was an independent predictor of not only cardiac death but also all-cause mortality in HF patients. HF patients who were underweight 1) had advanced HF and poorer nutrition, 2) had higher levels of TNF- α , adiponectin, troponin T, and pulmonary arterial pressure, and 3) had less RAS inhibitor and statin use, but more inotropic use. These statuses may in part affect the adverse prognosis of underweight HF patients.

Acknowledgements

The authors acknowledge the outstanding technical assistance of Ms. Kumiko Watanabe and Yuko Niimura.

Funding

This study was supported in part by a grant-in-aid for Scientific Research (No. 25461061) from the Japan Society for the Promotion of Science, and grants-in-aid from the Japanese Ministry of Health, Labor, and Welfare, Tokyo, Japan.

Conflict of interest

None.

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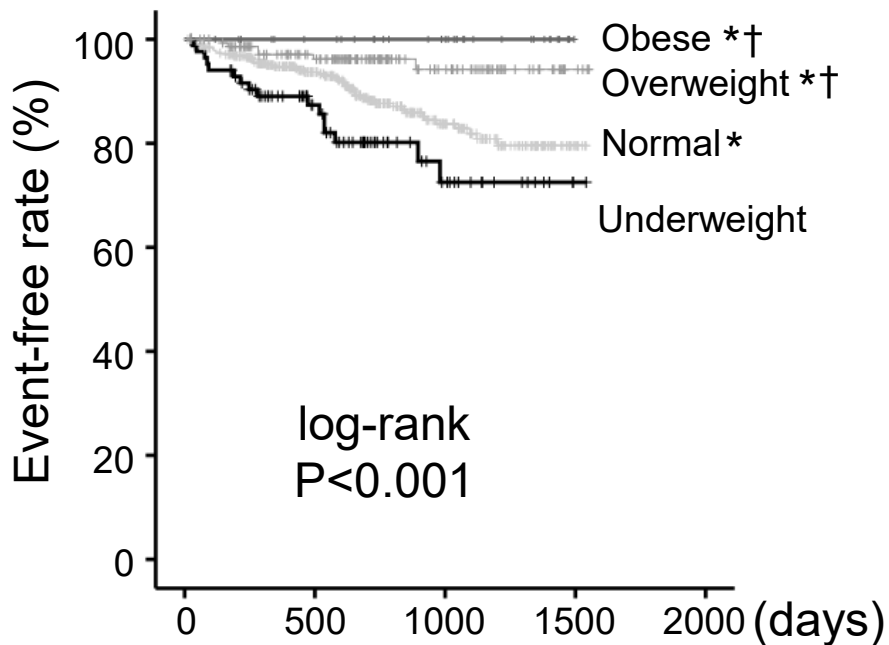
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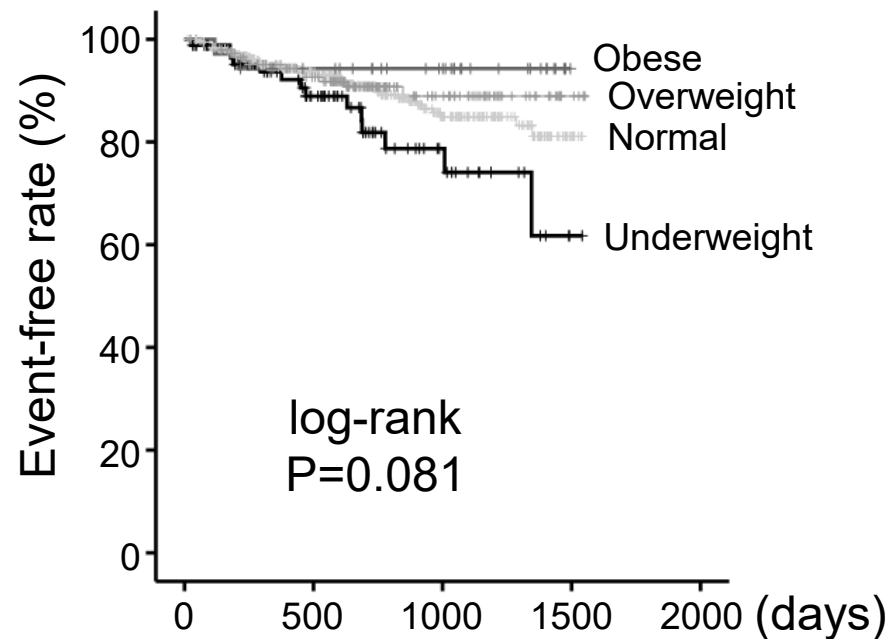
FIGURE LEGENDS

Figure 1 Kaplan-Meier analysis for A) cardiac mortality, B) non-cardiac mortality, and C) all-cause mortality among the four groups (Underweight, Normal, Overweight, and Obese group).

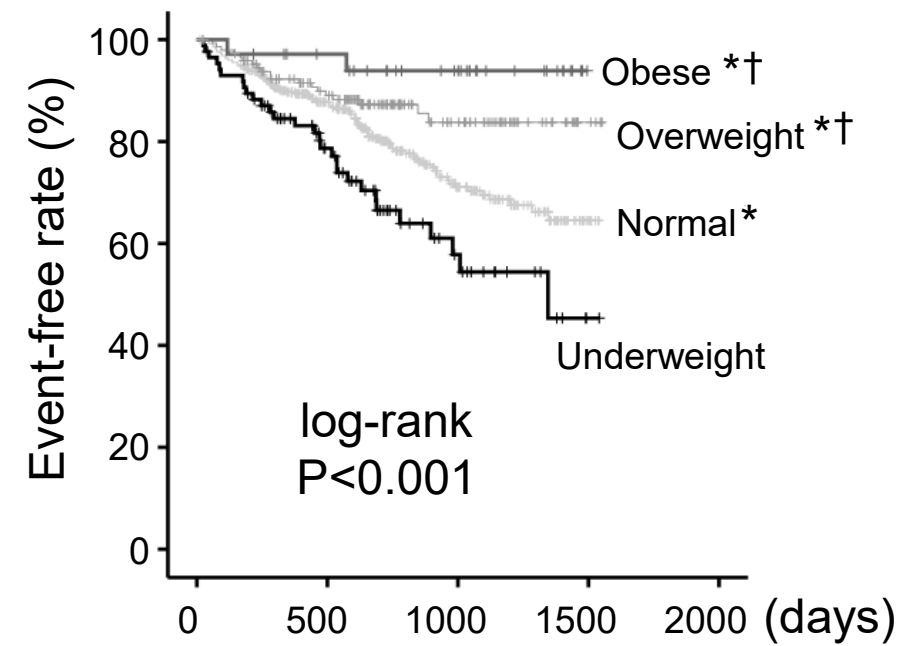
A) Cardiac mortality



B) Non-cardiac mortality



C) All-cause mortality



+ Underweight
 + Normal
 + Overweight
 + Obese

* P<0.05 vs. Underweight group

† P<0.05 vs. Normal group.